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The clinical course of COVID-19 in pregnant and non-pregnant women

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ABSTRACT

Aims: Pregnancy is a physiological condition that predisposes women to respiratory complications of viral infections thus, bringing the risk of developing more severe disease. The aim of this research was to elucidate the clinical course of COVID-19 in pregnant and non-pregnant women of childbearing age. Mortality rate, laboratory parameters, the occurence of cytokine storm in both groups and the response to treatment have been investigated.

Methods: A total of 88 women of childbearing age with a diagnosis of COVID-19 disease has been retrospectively analyzed. Age, comorbidity, length of stay in the intensive care unit and treatment regimen of patients have been obtained from hospital database. Ferritin, IL-6, CRP, procalcitonin, D-dimer, urea, creatinine, GFR, ALT, AST, LDH, lymphocyte count, neutrophil count, white blood cell count were evaluated. Clinical response such as reduction in oxygen requirement and vasopressor utilization before and after treatment were examined

Results: The rate of RT - PCR positive results were statistical significantly higher in pregnant women (p=0.003). The median WBC, lymphocyte and leukocyte values of the pregnant patients were higher (p=0.038, p=0.006 and p=0.035, respectively). The median hemoglobin, LDH and ferritin values of pregnant women were lower than those of non-pregnant individuals (p=0.032, p<0.001 and p=0.010, respectively). Mortality has been observed wit a rate of 17.5% in second trimester and 15% in the third trimester while 22.5% of women in the second trimester and 45% of women in the third trimester have survived COVID-19 infection.

Conclusion: Regarding the results of this study, we have observed differences in WBC, lymphocyte and leukocyte, median hemoglobin, LDH and ferritin values of pregnant women and non-pregnant individuals. Additionally, mortality rate was also comparable.

Keywords: COVID-19, pregnancy, mortality, D-dimer

INTRODUCTION

The novel Coronavirus disease (COVID-19), also called SARS-CoV-2, emerged as an urgent global public health problem, has rapidly spread to the rest of China and beyond into a pandemic after it was first reported in Wuhan, Hubei Province, China in December 2019.[1,2] In parallel with this, researches on COVID-19 have increased in every field and took their place in the literature.[3,4] The critical point in the management of any infectious disease is the care of the vulnerable population. It is known that pregnant women are disproportionately affected by respiratory diseases associated with increased infectious morbidity and maternal mortality rate.[5,6] According to the report by World Health Organization (WHO) on March 3, the predicted global mortality rate was 3.4% for COVID-19 infection.[7]

Pregnancy is a physiological condition that predisposes women to respiratory complications of viral infections. Infection of pregnant women with respiratory viruses due to physiological changes in the immune and cardio-pulmonary systems brings the risk of developing more severe disease. Virus infections are known to be responsible for serious complications during pregnancy, including endotracheal intubation, hospitalization in the intensive care unit (ICU), renal failure, and death.[5,6] The case fatality rate due to SARS-CoV infection in pregnant women is approximately 25%.[5] There is no evidence that COVID-19 causes intrauterine infection and creates a congenital infection, but it is difficult to make a definite decision due to the low number of cases.

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One of the largest series on COVID-19 in pregnancy is the study that included 215 pregnant patients during the New York pandemic attack.[8] SARS-CoV-2 positivity was detected at a rate of 15% in the screening performed in pregnant women (n=33) and it was stated that the majority of these patients were asymptomatic. Accordingly, it was reported that 13.5% of asymptomatic patients were found to be positive for SARS-CoV-2. In another study, it was observed that symptoms developed during labor or in the postpartum period in 71% of cases that were asymptomatic at presentation.[9]

United States Centers for Disease Control and Prevention, it was reported that the rate of asymptomatic cases in pregnant and non-pregnant patients was similar. Accordingly, 97.1% of pregnant women and 96.9% of non-pregnant women were symptomatic. In addition, the frequency of symptoms in pregnant and non-pregnant patients was similar.[10]

Pregnancy and birth in general, does not increase the risk of SARS-CoV-2 transmission and does not worsen the clinical course of COVID-19 disease compared to women of similar age who are not pregnant.[8,9] In most of the cases (>90%), mothers recover without the need for delivery.[11-15] However, considering age, underlying diseases and ethnicity in pregnant women, the rates of intensive care admissions were higher (1.5% vs. 0.9%; RR 1.5, 95% CI 1.2-1.8) and it was reported that the requirement for mechanical ventilation was more frequent (0.5% vs. 0.3%; RR 1.7, 95% CI 1.2-2.4) but mortality rates did not change.[10]

Again, in a study conducted in the United States, it was shown that 27% of pregnant women with COVID-19 were mild, 26% were seriously ill and 5% were critically ill.[16] In addition, serious disease is more common in late pregnancy.[17]

The frequency of preterm birth and cesarean section increases in cases with COVID-19 during pregnancy. Fever and hypoxemia may increase preterm labor due to premature rupture of membranes and abnormal fetal heart rate patterns. However, preterm birth can be seen in patients without serious respiratory disease. In a systematic review examining 790 cases who had COVID-19 during pregnancy, the delivery rate before 37 weeks was reported as 23% (OR: 2.28, 95% CI 0.92-5.65) and the cesarean rate was 72%.[18] In a study conducted in the United Kingdom involving 427 pregnant COVID-19 patients, the rate of preterm delivery was reported as 27% and the rate of cesarean section as 59%.[19] However, most of the preterm deliveries were iatrogenic rather than spontaneous.[20]

Although data on the first trimester are limited, the risk of spontaneous abortion does not seem to increase in pregnant women with COVID-19.[15,21]

The aim of this research was to elucidate the clinical course of COVID-19 in pregnant and non-pregnant women of childbearing age. Mortality rate, laboratory parameters, the occurence of cytokine storm in both groups and the response to treatment have been investigated.

METHODS

The study was carried out with the permission of the Ankara City Hospital No:1 Clinical Researches Ethics Committee (Date: 12/01/2022, Decision No: E1-22-2293). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study was designed as a single-center and retrospective study. Patients over the age of 18 years, who have been admitted to our institution between 01.03.2020 and 01.03.2022 with a confirmed reverse transcription -polymerase chain reaction (RT - PCR) result and radiologic findings have been included in this research.

Age, comorbidity, length of stay in the intensive care unit and treatment regimen of pregnant and non-pregnant female patients of childbearing with a confirmed diagnosis of COVID-19 have been obtained from hospital database.

Ferritin, interleukin-6 (IL-6), C-reactive protein (CRP), procalcitonin, D-dimer, urea, creatinine, glomerular filtration rate (GFR), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), white blood cell (WBC) count, lymphocyte count, neutrophil count, and platelet count were evaluated.

Clinical response such as reduction in oxygen requirement and vasopressor utilization before and after treatment were examined. In addition, mortality rate, laboratory parameters, the occurence of cytokine storm in both groups and the response to treatment have been investigated.

Inclusion and Exclusion Criteria

Women over 18 years of age, with childbearing potential who had a confirmed diagnosis of COVID-19 via laboratory and radiologic parameters have been enrolled in this study. Women out of childbearing age, individuals who had passed 14 days after RT - PCR positivity on post-covid period have been excluded from the study.

Data Analysis and Statistics

Shapiro Wilk test was utilized for assessing whether the variables follow normal distribution or not. Continuous variables were presented as median (minimum:maximum) and mean±standard deviation values. Categorical variables were reported as n (%). According to the normality test results, Independent sample t test or Mann Whitney U test was used in comparison between two groups. Pearson Chi-square test, Fisher's exact test and Fisher Freeman Halton Test were used for comparing categorical variables. SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0, Armonk, NY: IBM Corp.) was used for statistical analysis and. A p value <0.05 was considered statistically significant.

RESULTS

A total of 88 women of childbearing age with a diagnosis of COVID-19 disease has been retrospectively analyzed (Figure).

The comparison of age, RT - PCR result, computed tomography (CT), treatment and laboratory parameters have been elaborated in Table 1. When the table was examined, no statistically significant difference was found between the groups in terms of age distribution (p=0.096). There was a statistical significance between the groups according to the RT - PCR results, and it was seen that the rate of those with positive PCR results was higher in the pregnant women (p=0.003).

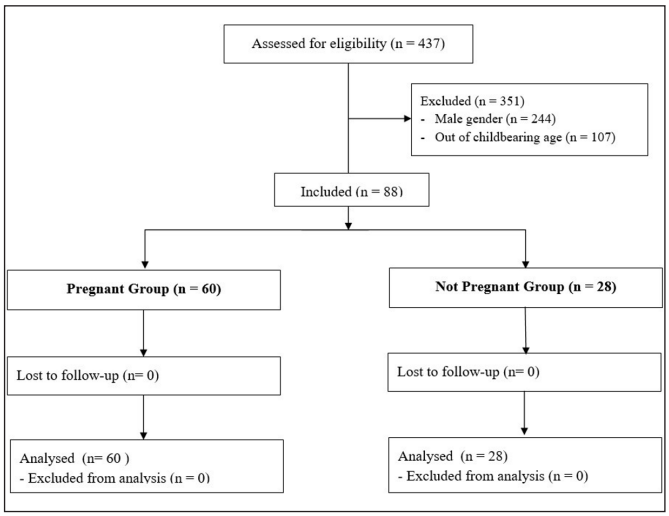
Assessed for eligibility (n = 437)
Excluded (n = 351)
- Male gender (n = 244)
- Out of childbearing age (n = 107)
Included (n = 88)
Pregnant Group (n = 60)
Not Pregnant Group (n = 28)
Lost to follow-up (n= 0)
Lost to follow-up (n= 0)
Analysed (n= 60)
- Excluded from analysis (n = 0)
Analysed (n = 28)
- Excluded from analysis (n = 0)

Figure. Flow chart of the patients.

Table 1: Comparison of demographic and clinical characteristics between pregnant and non-pregnant patient groups

	n	Pregnant	n	Non Pregnant	p-value
Age (years)	60	29 (23:40)	28	34.50 (20:39)	0.096[a]
RT - PCR	60		28		0.003[b]
Positive		56 (93.33%)		19 (67.86%)	
Negative		4 (6.67%)		9 (32.14%)	
CT Result	21		25		>0.99[b]
COVID-19 findings		20 (95.24%)		23 (92%)	
No COVID-19 findings		1 (4.76%)		2 (8%)	
WBC	60	9.35 (4.10:29.60)	28	6.61 (2.35:37.60)	0.038[a]
Lymphocyte	60	0.75 (0.15:4.50)	28	0.62 (0.14:1.25)	0.006[a]
Neutrophil	60	7.65 (2.79:26.30)	28	5.65 (1.94:35.60)	0.035[a]
Platelet	60	295.50 (99:720)	28	268.50 (58:478)	0.284[a]
Hemoglobin	60	11.20 (5.70:15.20)	28	11.80 (4.60:15.70)	0.032[a]
AST	60	41 (12:733)	28	43.50 (12:237)	0.893[a]
ALT	60	25.50 (5:550)	28	25 (6:310)	0.788[a]
LDH	60	383.50 (213:3821)	28	529 (314:1081)	<0.001[a]
Ferritin	60	84.50 (11:1748)	28	177 (10:1075)	0.010[a]
CRP	60	83 (0.20:198)	28	73.50 (25:218)	0.230[a]
IL - 6	60	12.50 (2:1000)	28	10 (2:1360)	0.943[a]
D - dimer	60	1.73 (0.19:31)	28	1.21 (0.29:26)	0.081[a]
H SCORE	58	2 (0:4)	28	2 (1:5)	0.989[a]
PCT	60	0.13 (0.02:3.70)	28	0.06 (0.02:36)	0.114[a]
Steroid usage	59		28		0.436[c]
dxm		2 (3.39%)		1 (3.57%)	
40 mg		8 (13.56%)		1 (3.57%)	
80 mg		7 (11.86%)		4 (14.29%)	
250 mg		24 (40.68%)		9 (32.14%)	
>250 mg		12 (20.34%)		8 (28.57%)	
yok		4 (6.78%)		5 (17.86%)	

Data are expressed as n (%) and median (minimum:maximum). a: Mann Whitney U Test, b: Fisher's Exact test, c: Fisher Freeman Halton Test, COVID-19: Coronavirus disease 2019; RT - PCR: reverse transcription - polymerase chain reaction; IL-6: interleukin-6; CRP: C-reactive protein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; WBC: white blood cell ; CT: computed tomography; PCT: procalcitonin

It was determined that there was a statistically significant difference between the groups in terms of WBC, lymphocyte, leukocyte, hemoglobin, LDH and ferritin values. It is observed that the median WBC, lymphocyte and leukocyte values of the pregnant patients were higher (p=0.038, p=0.006, and p=0.035, respectively). The median hemoglobin, LDH and ferritin values of pregnant women were lower than those of non-pregnant individuals (p=0.032, p<0.001, and p=0.010, respectively). No statistically significant difference was found in the comparisons of other variables included in Table 1 (p>0.05).

There was no statistically significant difference between the groups in terms of treatment intervention. Entubation, Continuous Renal Replacement Therapy (CRRT), hemodiafiltration (HDF), Extracorporeal membrane oxygenation (ECMO), non - invasive mechanical ventilation (NIMV), vasopressor inotropic usage variables did not differ between the groups (Table 2) (p>0.05). Since the number of patients who underwent mechanical ventilation (MV) in the study groups was insufficient for statistical comparison, no significance has been achieved. Additionally, mortality, bacterial colonisation, onset of symptoms, duration of MV and ICU stay was comparable between pregnant and non - preganant women (Table 2).

There was no statistically significant difference between the number of patients in the 2nd and 3rd trimesters, post - partum period or non - pregnant women (Table 3) (p>0.05).

Majortiy of the patients (75%) had no comorbidity, while asthma has been observed in 5.68% individuals, diabetes mellitus 2.27% and hypothyroidism in 2.27% of the enrolled subjects (Table 4).

The mortality rate of pregnant women has been denoted in Table 5. When the table was examined, mortality has been observed in 17.5% in second trimester and 15% in the third trimester while 22.5% of women in the second trimester and 45% of women in the third trimester have survived COVID-19 infection.

Table 3. Pregnancy status of study population

	n=88
2nd trimester	16 (18.18%)
3rd trimesters	24 (27.27%)
Post-partum	20 (22.73%)
Non Pregnant	28 (31.82%)

Data are expressed as n(%).

Table 2. Interventions applied to treatment groups

	n	Pregnant	n	Non Pregnant	p value
Entubation	60		28		0.134[d]
No		20 (33.33%)		5 (17.86%)	
Yes		40 (66.67%)		23 (82.14%)	
NHFO	60		28		0.732[d]
No		49 (81.67%)		22 (78.57%)	
Yes		11 (18.33%)		6 (21.43%)	
NIMV Requirement	59		28		>0.99[b]
No		4 (6.78%)		2 (7.14%)	
Yes		55 (93.22%)		26 (92.86%)	
Vasopressor inotropic usage	60		28		0.414[d]
No		13 (21.67%)		4 (14.29%)	
Yes		47 (78.33%)		24 (85.71%)	
HDF	60		28		0.318[b]
No		0		1 (3.57%)	
Yes		60 (100%)		27 (96.43%)	
CRRT	60		28		0.538[b]
No		1 (1.67%)		1 (3.57%)	
Yes		59 (98.33%)		27 (96.43%)	
ECMO	60		28		0.173[b]
No		5 (8.33%)		0	
Yes		55 (91.67%)		28 (100%)	
Mortality	60		28		0.197[d]
Survived		44 (73.33%)		24 (85.71%)	
Deceased		16 (26.67%)		4 (14.29%)	
Bacterial Colonisation	60		28		0.478[d]
No		21 (35%)		12 (42.86%)	
Yes		39 (65%)		16 (57.14%)	
Onset of symptoms	60	5 (1:17)	28	4 (1:10)	0.101[a]
Duration of MV*	20	4.50 (1:28)	4	13.50 (4:35)	-
ICU Stay	60	6 (1:40)	28	7.5 (2:50)	0.261[a]

Data are expressed as n (%) and median (minimum:maximum). a: Mann Whitney U Test, b: Fisher's Exact test, d:Pearson Chi-Square Test, * Since the number of units was insufficient for statistical analysis, comparisons between groups could not be made. HFNO: high-flow nasal oxygen; CRRT: Continuous Renal Replacement Therapy; HDF: hemodiafiltration; ECMO: Extracorporeal membrane oxygenation; NIMV: non - invasive mechanical ventilation; MV: mechanical ventilation; ICU: intensive care unit

Table 4. Comorbid diseases of the study population

	n=88
Asthma	5 (5.68%)
Multipl Cerebral Infarct +Aortic Vegetation + HIV+	1 (1.14%)
DM	2 (2.27%)
DM (Diabetic Ketoacidosis)	1 (1.14%)
Down Syndrome	1 (1.14%)
Hypothyroidism	2 (2.27%)
Hypertension	1 (1.14%)
Hyperteinsion+CRF+Mental Retardation	1 (1.14%)
Valve Replacement	1 (1.14%)
Malignancy (Cured lymphoma)	1 (1.14%)
Obesity	1 (1.14%)
SLE	1 (1.14%)
Thalassemia Carrier	1 (1.14%)
Long QT Syndrome	1 (1.14%)
None	66 (75%)

Data are expressed as n(%). DM: diabetes mellitus; SLE: Systemic lupus erythematosus; CRF: chronic renal failure.

Table 5. Mortality, duration of MV, ICU stay and H SCORE with respect to gestational period

	n	2nd Trimester	n	3rd Trimester	p value
Mortality	16		24		0.215[d]
Survived		9 (22.50%)		18 (45%)	
Deceased		7 (17.50%)		6 (15%)	
Duration of MV	8	3 (1:24)	8	4.50 (1:19)	0.798[a]
ICU Stay	16	5.50 (1:31)	24	7 (2:28)	0.576[a]
H SCORE	16	2.31±1.40	22	2±1.07	0.440[e]

Data are expressed as n (%), median (minimum:maximum) and mean±standard deviation. a: Mann Whitney U Test, d:Pearson Chi-Square Test, e: Independent Sample t Test, ICU: intensive care unit; MV: mechanical ventilation.

DISCUSSION

Due to its physiological structure, the pregnancy period reduces the defense of women against viral infections and suppresses the immune system. It is known that pregnant women have an increased risk of morbidity and mortality in respiratory tract infections such as influenza. Therefore, pregnant women are considered to be a risky group for COVID-19.[22] In a large international systematic review, it was found that the mortality rate of pregnant women with COVID-19 was not high, but their care needs were increased.[23] In published articles it has been determined that COVID-19 causes complications such as premature rupture of membranes, preterm labor and fetal distress in pregnant women.[23,24]

It has been reported that premature rupture of membranes develops, and an emergency cesarean section was performed in one pregnant woman due to preterm labor. In a study conducted by Zhu et al.[25] in nine pregnant women with COVID-19, fetal distress was reported in six of them. In this context, pregnant women infected with COVID-19 should be followed closely by healthcare professionals in terms of possible complications.

Although it has been reported that pregnant women in the third trimester are at higher risk, it has also been reported that maternal deaths from COVID-19 are not at an alarming level.[26,27] In a study examining the effect of severe acute respiratory syndrome on pregnancy, it was reported that, diseases that cause severe respiratory symptoms may trigger fetal death, miscarriage, and congenital anomalies during early pregnancy.[28] In addition, in a study conducted in the United Kingdom, the maternal mortality rate was found to be 5.8/100.000.[19] In this study mortality has been d observed in 17.5% in second trimester and 15% in the third trimester, while 22.5% of women in the second trimester and 45% of women in the third trimester have survived COVID-19 infection.

It is recommended to perform CT and RT-PCR tests in the diagnosis of COVID-19, and it is reported that both should be performed in order to establish the definitive diagnosis in the most reliable way.[29] Ground glass opacities detected on CT are found in most patients with COVID-19 and recommended for diagnosis. Exposure of the fetus to radiation in CT is very low.[30,31] Despite this, American College of Obstetricians and Gynecologists recommends that CT should be performed by protecting the abdomen when necessary.[32] In this study there was a statistical significance between the groups according to the RT - PCR results, and it was seen that the rate of those with positive PCR results was higher in the pregnant women.

Studies have shown that increased amounts of proinflammatory cytokines in serum are associated with pulmonary inflammation and extensive lung injury. The severity of the cytokine storm may be one of the mechanisms involved in the occurrence, development and prognosis of COVID-19. Complete blood count, IL-6, D-dimer and other laboratory parameters can be stated as an important predictor of inflammatory progression both in the diagnosis of COVID-19 and in intensive care hospitalization.[33] In studies with COVID-19 it was observed that while mild WBC increase was observed in patients with severe disease symptoms, there was a significant increase in patients who were deceased. The increase in leukocyte levels can be counted as a parameter that shows the deterioration of the clinic. In addition to leukocytosis, an increase in neutrophils and a decrease in lymphocytes, monocytes and eosinophils were found in various studies.[34] In this study we have observed that the median WBC, lymphocyte and leukocyte values of the pregnant patients were statistically higher than non-pregnan women.

Cytokin storm plays an important role in critical patient groups with SARS-CoV-2 infection which is mainly characterized by elevated plasma IL-6 levels.[33] According to recent COVID-19 studies it was elaborated that the level of IL-6 in the severe group was higher than that in the moderate group, suggesting that IL-6 can be used as a biomarker for severity assessment.[35] However, the correlation of IL-6 levels in critically ill patients is still unknown. It the current study the decrease IL-6 levels after COVID-19 in the group with mortality was significantly higher compared to pre-COVID-19 levels. In this study there was no difference in the occurence of cytokine storm between pregnant and non-pregnant patients.

Ferritin, a protein that functions as an iron storage, increases as a result of the activation of macrophages and hepatocytes in COVID-19. Unlike other viral infections, ferritin shows a moderate increase in cytokine storm syndrome. It is thought that it can be used as a predictive marker in sepsis mortality. In the current study, ferritin decreased in the group with mortality while it increased

in the group without mortality.[36] In this study there was a statistically significant difference between the groups in terms of WBC, lymphocyte, leukocyte, hemoglobin, LDH and ferritin values. The median hemoglobin, LDH and ferritin values of pregnant women were lower than those of non-pregnant individuals (p=0.032, p<0.001, and p=0.010, respectively).

Hypercoagulopathy is associated with the severity of COVID-19 symptoms, and D-dimer levels are one of the main parameters to consider when evaluating coagulopathy in COVID-19 patients. As COVID-19-associated coagulopathy differs from disseminated intravascular coagulation, high D-dimer levels are strongly associated with disease severity and increased mortality, so it is necessary to closely monitor the dynamics of coagulation parameters in COVID-19 patients. In the current study D - dimer level decreased in the mortality group and increased in the group without mortality.[37]

There is no meaningful data published yet on how pregnancy is affected in the first trimester. Influenza virus has been reported to increase abortion rates.[38] In the following weeks of pregnancy, based on studies on other viral infections, complications up to perinatal mortality can be expected in the presence of COVID-19.[39] In general, cases with mild infections are also common in pregnant women. About 15% of asymptomatic cases are reported. Almost all patients undergoing radiological imaging have pneumonia findings. An increased incidence has been reported, especially in preterm birth rates. However, there is no evidence of an increased incidence of preeclampsia.[40] In this study majortiy of the patients (75%) had no comorbidity, while asthma has been observed in 5.68% individuals, diabetes mellitus 2.27% and hypothyroidism in 2.27% of the enrolled subjects.

This study has limitations. The main limitation of this study could be attributed to its retrospective nature. The relatively small sample size could be another limitation.

CONCLUSION

Regarding the results of this study, we have observed differences in WBC, lymphocyte and leukocyte, median hemoglobin, LDH and ferritin values of pregnant women and non-pregnant individuals. Additionally, mortality rate was also comparable.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Ankara City Hospital No:1 Clinical Researches Ethics Committee (Date: 12/01/2022, Decision No: E1-22-2293).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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